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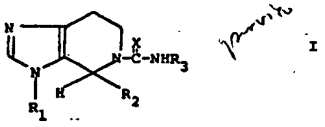
(54) TETRAHYDRO-IMIDAZO-PYRIDINE DERIVATIVES

(71) We, SOCIETA FARMACEUTICI ITALIA SPA, a Body Corporate organised and existing under the laws of Italy, of 1/2 Largo Guido Donegani-1 20121 Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to new 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine derivatives.

The invention provides new derivatives of general formula I:



I

wherein R_1 is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R_2 is a hydrogen atom, or an alkyl group having from 1 to 4 carbon atoms, or a cycloalkyl, aryl or heteroaryl group, R_3 is a hydrogen atom, an alkyl or alkenyl group having from 1 to 6 carbon atoms or a cycloalkyl group having from 3 to 6 carbon atoms or an aromatic group, X is S, O, or NR_4 where R_4 is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, an amino, cyano, nitro, or acylamino group, or a pharmaceutically acceptable acid addition salt thereof.

The invention includes a process of preparing these compounds which comprises condensing an appropriate 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine with an appropriate alkyl isocyanate, alkyl isothiocyanate or substituted S-methyl isothiourea, in ethanol, acetonitrile or dioxan as solvent, under reflux for from 4 to 12 hours. The products can be isolated by crystallization as free bases or as salts of pharmaceutically acceptable acids.

The new compounds of the invention have proved well tolerated and to inhibit both the number of experimental ulcers and the gastric secretion in experimental animals. Thus they should prove useful in the therapy of gastric and duodenal ulcers in man.

The activity of these compounds has been assessed in rats in anti-ulcer and anti-secretory tests. Methiamide, which is well known for its antisecretory activity (Wyllie et al: Gut, 1973, *14*, 424), was adopted as reference standard.

1. *Inhibition of restraint ulcer in rats* (Bonfils et al., Thérapie, 1960, *15*, 1096). Six Sprague-Dowley male rats (100—120 g) fasted for 24 hours were used for each group. A square flexible small-mesh wire netting was used for immobilization. After 4 hours immobilization the rats were sacrificed, their stomachs were removed, and lesions counted under a dissecting microscope. The compounds were administered subcutaneously (s.c.) (10 mg/kg) immediately before the immobilization or orally (os) (50 mg/kg) one hour before.

2. *Inhibition of gastric secretion in rats* (Shay, Gastroenterology, 1945, *43*, 5). Gastric antisecretory activity was evaluated in rats by the pylorus ligature technique. Six Sprague-Dowley male rats (110—130 g) were used for each group. Twenty-four hours before the test, the rats were deprived of food but their water supply was maintained. On the day of the operation, the pylorus was ligated under light ether anesthesia. Four hours after the ligature, the rats were sacrificed, the stomach secretion was collected and centrifuged at 3500 r.p.m. for 10 minutes, and the volume, less sediment, was determined. The amount

f the free hydrochloric acid in the gastric juice was determined by titration against 0.01 N sodium hydroxide using Töpfer's Indicator. Each compound, at a dose of 50 mg/kg was injected subcutaneously at the time of ligature. In Table I, are shown the results obtained expressed as ED_{50}. The compound reference numbers are explained in the Examples below.

TABLE I

Compound	Antiulcer		Antisecretory
	s.c.	os	s.c.
Methiamide	14	64	60
386/1087	0.9	3.1	6
1068	0.6	2.4	50
1116	10	34	23
1184	0.64	11	22
1286	0.85	8.5	34
1287	19	50	50
1293	6	25	8
1359	5	1.8	40
1360	10	5.6	19
1361	10	25	50
1367	3.3	6	50
1316	0.75	6.6	50
1348	0.1	0.55	18
1350	6.5	5.6	50
1365	2	3.8	50
1366	0.75	3.8	17

As many antiulcer agents display a remarkable anticholinergic activity, some derivatives have been also orally assessed for their antagonism against cromodacriorrhea induced by carbacholine in rats (Winburg M. et al.: J. Pharm. Exp. Therap., 1949, *95*, 53). Table II shows the ratios between the ED_{50}s for the anticholinergic and antiulcer activity. Some derivatives display an antiulcer activity at doses 5 to 25 times lower than anticholinergic activity. For both atropine and methiamide the ratio is about 2.

TABLE II

Compound	Anticholinergic Activity	Anticholinergic ED_{50} / Antiulcer ED_{50}
Atropine	0.8	2
Methiamide	85	1.33
386/1286	50	5.88
/1359	45.5	25.28
/1360	76	13.57
/1316	70	10.61
/1348	7.8	14.18
/1350	100	17.86
/1365	21	5.53

The invention is illustrated by the following Examples in which all temperatures are in degrees Celsius (C).

Example 1.

5 - (N - methyl - thiocarbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine ($R_1=R_2=H$; $R_3=CH_3$) (386/1068). A solution of 1 g of 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine (Farmaco, Ed. Sci., 1967, *22*, 821) and 0.65 g of methyl isothiocyanate in 20 ml of ethanol are refluxed for 8 h. The solution is cooled and filtered: 1.15 g of 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine, m.p. 228°, are collected.

Example 2.

5 - (N - ethyl - thocarbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine ($R_1=R_2=H$; $R_3=C_2H_5$) (386/1293). A soluton of 1.85 g of 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine and 2 g of ethyl isothiocyanate in 15 ml of acetonitrile are refluxed for 7 h. The solution is cooled and filtered: 2.5 g of 5-[N-ethyl-thiocarbamoyl]-4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine, m.p. 185°, are collected.

Example 3.

5 - (N - *n* - propyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine ($R_1=R_2=H$; $R_3=C_3H_7$). Operating as in Example 1, but employing propyl isothiocyanate, the product is obtained in 81% yield. m.p. 151°, (386/1361).

Example 4.

5 - (N - *iso*propyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine ($R_1=R_2=H$; $R_3=i-C_3H_7$) (386/1087). A solution of 2 g of 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine hydrochloride and 2.5 g of isopropyl isothiocyanate in 20 ml of acetonitrile and 5 ml of ethanol is refluxed 8 h. Evaporation of the solvent leaves a residue that is treated with one equivalent of ethanolic hydrogen chloride. Evaporation of the solvent leaves a residue which is crystallized from acetone to give 2.5 g of 5 - (N - *iso*propyl - thiocarbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine hydrochloride, m.p. 170°.

Example 5.

5 - (N - *n* - butyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine ($R_1=R_2=H$; $R_3=n-C_4H_9$). Operating as in Example 1, but employing butyl isothiocyanate the product is obtained in 75% yield. m.p. 80° (386/1331).

Example 6.

5 - (N - cyclohexyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine ($R_1=R_2=H$; $R_3=$cyclohexyl) (386/1294). Operatng as in Example 2, but employing cyclohexyl isothiocyanate the product, m.p. 183°, is obtained in 82% yield.

Example 7.

4 - Ethyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-6-pyridine ($R_1=H$; $R_2=C_2H_5$; $R_3=CH_3$) (386/1214). A soluton of 2.9 g of 4 - ethyl - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (Farmaco, Ed. Sci. 1967, *22*, 821) and 3 g of methyl isothiocyanate

in 32 ml of acetonitrile and 8 ml of ethanol refluxed for 8 h. The solution is evaporated in vacuo, and the residue crystallized from diethyl ether to give 3 g of 4-ethyl-5-(N-methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine, m.p. 230°.

Example 8.

5 - (N - allyl - thiocarbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine ($R_1=R_2=H$; R_3=allyl) (386/1185). Operating as in Example 2, but employing allylisothiocyanate, the product, m.p. 172°, is obtained in 71% yield.

Example 9.

4 - Ethyl - 5 - (N - *iso*propyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine ($R_1=H$; $R_2=C_2H_5$; $R_3=i\text{-}C_3H_7$) (386/1184). Operating as in Example 7, but employing isopropyl isothiocyanate, the product, m.p. 215°, is obtained in 79% yield.

Example 10.

4 - Ethyl - 5 - (N - allyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine ($R_1=H$; $R_2=C_2H_5$; R_3=allyl) (386/1216). Operating as in Example 7, but employing allyl isothiocyanate, the product, m.p. 205°, is obtained in 70% yield.

Example 11.

4 - Ethyl - 5 - (N - butyl - thiocarbamoyl)-4,5,6,7 - tetrahydroimidazo - [4,5 - c]-pyridine ($R_1=H$; $R_2=C_2H_5$; $R_3=n\text{-}C_4H_9$) (386/1215). Operating as in Example 7, but employing butyl isothiocyanate, the product, m.p. 180°, is obtained in 75% yield.

Example 12.

4 - Phenyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine ($R_1=H$; $R_2=C_6H_5$; $R_3=CH_3$) (386/1254). A solution of 3.5 g of 4 - phenyl - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine (Farmaco, Ed. Sci., 1967, *22*, 821) and 3.5 g of methyl isothiocyanate in 55 ml of dioxan is refluxed for 4 h. The solution is cooled and filtered: 3.6 g of 4 - phenyl - 5 - (N - methyl-thiocarbamoyl) - 4,5,6,7 - tetrahydroimidazo-[4,5-c]-pyridine, m.p. 228°, are collected.

Example 13.

4 - Phenyl - 5 - (N - isopropyl - thiocarbamoyl) - 4,5,6,7 - tetrahydroimidazo-[4,5-c]-pyridine ($R_1=H$; $R_2=C_6H_5$; $R_3=i\text{-}C_3H_7$) (386/1253). Operating as in Example 12, but employing isopropyl isothiocyanate, the product, m.p. 198°, is obtained in 80% yield.

Example 14.

4 - *iso* - propyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine ($R_1=H$; $R_2=i\text{-}C_3H_7$; $R_3=CH_3$) (386/1257). To a solution of 20 g of histamine dihydrochloride in 54 ml of water and 440 ml of methanol, 19.6 g of sodium hydroxide dissolved in 54 ml of water and 25 ml of *iso*butyraldehyde are added and the solution refluxed for 24 h. The solution is then acidified with 200 ml of conc. hydrochloric acid and evaporated in vacuo. The residue is taken up in methanol. The methanolic extract is evaporated in vacuo to give 23 g of 4-*iso*propyl-4,5,6,7-tetrahydro-imidazo - [4,5-c] - pyridine dihydrochloride, m.p. 238°, from which the free base, m.p. 112°, is obtained by ion-exchange on Amberlite (Trade Mark) IRA 410. A solution of 1.3 g of the base in 10 ml of dioxan is treated with 1.3 g of methyl isothiocyanate and refluxed for 4 h. The solution is cooled and filtered; 1.4 g of 4-*iso*propyl-5-(N-methyl-thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine, m.p. 240°, are collected.

Example 15.

4 - *iso* - propyl - 5 - (N - *iso*propyl - thi - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine ($R_1=H$; $R_2=R_3=i\text{-}C_3H_7$) (386/1258). Operating as in Example 14, but employing *iso*propyl isothiocyanate, the product, m.p. 203°, is obtained in 80% yield.

Example 16.

3 - Methyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine ($R_1=R_3=CH_3$; $R_2=H$) (386/1276). A solution of 1 g of 3-methyl-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine and 1 g of methyl isothiocyanate in 10 ml of acetonitrile is refluxed for 4 h. The solution is cooled and filtered: 0.9 g of 3-methyl - 5 - (N - methyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine, m.p. 235°, are collected.

Example 17.

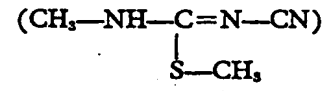
3 - Methyl - 5 - (N - *iso*propyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine ($R_1=CH_3$; $R_2=H$; $R_3=i\text{-}C_3H_7$) (386/1286). Operating as in Example 16, but employing *iso*propyl isothiocyanate, the product, m.p. 205°, is obtained in 66% yield.

Example 18.

5 - (N - Phenyl - thiocarbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine ($R_1=R_2=H$; $R_3=C_6H_5$) (386/1116). Operating as in Example 2, but employing phenyl isothiocyanate, the product, m.p. 205°, is obtained in 82% yield.

Example 19.

5 - (N - cyano - N' - methyl - amidino)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1347). A solution of 1.23 g of 4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine and 1.29 g of N,S-dimethyl-N'-cyano-isothiourea



in 15 ml of acetonitrile is refluxed for 21 h. After evaporation to dryness, chromatography on silica gel (ethyl acetate-ethanol as eluant) of the residue gives 630 mg of the pure title compound, m.p. 240°C.

Example 20.

5 - Amidino - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine (386/1289). A solution of 1.23 g of 4,5,6,7 - tetrahydro-imidazo - [4,5 - c] - pyridine and 0.9 g of S-methyl-isothiourea in 15 ml of acetonitrile is refluxed for 8 h. After evaporation to dryness, the residue is treated with one equivalent of ethanolic hydrogen chloride. After cooling, 1.4 g of 5-amidino-4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine monohydrochloride, m.p. 310°, are collected.

Example 21.

4 - Ethyl - 5 - amidino - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine (386/1284). Operating as in Example 20, 1.5 g of 4 - ethyl - 5 - guanyl - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine monohydrochloride, m.p. 300°C (dec.) are obtained from 1.51 g of 4-ethyl-4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

Example 22.

4 - Ethyl - 5 - (N - ethyl - amidino)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1336). A solution of 1.51 g of 4 - ethyl - 4,5,6,7 - tetraidro - imidazo-[4,5-c]-pyridine and 1.18 g of N-ethyl-S-methyl-isothiourea in 15 ml of acetonitrile is refluxed for 8 h. After evaporation to dryness the residue is treated with one equivalent of ethanolic hydrogen bromide. After cooling, 1.5 g of 4-ethyl-5-(N-ethyl-amidino)-4,5,6,7-tetraidro - imidazo - [4,5 - c] - pyridine monohydrobromide, m.p. 275°C, are collected.

Example 23.

4 - Ethyl - 5 - (N - *iso*propyl - amidino)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1337). Operating as in Example 22, but employing N-*iso*propyl-S-methyl-isothiourea, 1.6 g of 4-ethyl-5-(N-*iso*propyl-amidino) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine monohydrobromide (m.p. 280°C (dec.)) are obtained.

Example 24.

5 - (N - ethyl - amidino) - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine. Operating as in Example 22, the monohydrobromide of the title compound is obtained in 50% yield from 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

Example 25.

5 - (N - *iso*propyl - amidino) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine. Operating as in Example 23, the monohydrobromide of the title compound is obtained in 55% yield from 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

Example 26.

4 - Phenyl - 5 - (N - methyl - carbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1261). A solution of 3 g of 4 - phenyl - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine and 3.42 g of methyl isocyanate in 40 ml of dry dioxan is refluxed for 1.5 h. Evaporation to dryness gives a solid (4.72 g) that is washed with some ethyl acetate, dissolved in 60 ml of methanol and treated with 15 ml of 2N sodium hydroxide for 2 h at room temperature. After neutralization, the solution is extracted with chloroform. Evaporation of the solvent leaves a residue that is taken up in ethyl acetate to give 2.5 g of the title compound, m.p. 180°C.

Example 27.

4 - Phenyl - 5 - (N - *iso*propyl - carbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1351). Operating as in Example 26, but employing *iso*propyl isocyanate, 3.11 g of the title compound, m.p. 245°C, are obtained.

Example 28.

4 - Ethyl - 5 - (N - methyl - carbamoyl-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1295). A solution of 1.51 g of 4 - ethyl - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine and 2.28 g of methyl isocyanate in 20 ml of dry dioxan is refluxed for 1.5 h. The solution is cooled and filtered. The solid collected is dissolved in 30 ml of methanol and treated with 7 ml of 2N sodium hydroxide for 2 h at room temperature. After neutralization the solution is extracted with chloroform. Evaporation of the solvent leaves a residue that is taken up in ethyl acetate 1.05 g of the title compound, m.p. 240°C, are collected.

Example 29.

4 - Ethyl - 5 - (N - *iso*propyl - carbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1316). Operating as in Example 28, employing *iso*propyl isocyanate the title compound, m.p. 170°C, is obtained in 70% yield.

Example 30.

5 - (N - methyl - carbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine (386/1350). Operating as in Example 28, 1.8 g of the title compound, m.p. 213°C, are obtained from 2.46 g of 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

Example 31.

5 - (N - *iso*propyl - carbamoyl - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine (386/1348). A solution of 2.46 g of 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine and 6.8 g of *iso*propyl isocyanate in 50 ml of dry dioxan is refluxed for 2 h. After evaporation to dryness, the residue is dissolved in 25 ml of methanol and treated with 12.5 ml of 2N sodium hydroxide for 2 h at room temperature. After neutralization, the solution is extracted with chloroform. Evaporation of the solvent leaves a residue (2.21 g, oil) that is treated with one equivalent of hydrogen chloride in isopropanol. After cooling, 1.7 g of 5 - (N - *iso*propyl - carbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4, 5- c] - pyridine hydrochloride, m.p. 190°C, are collected.

Example 32.

5 - (N - cyclopropyl - carbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine (386/1365). A solution of 3.69 g of 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine and 7.47 g of cyclopropyl isocyanate in 20 ml of dry dioxan is refluxed for 1.5 h. After evaporation to dryness, the residue is dissolved in 44 ml of methanol and treated with 11 ml of 2N sodium hydroxide for 1.5 h at room temperature. After neutralization, the solution is extracted with chloroform. Evaporation of the solvent leaves a residue that is taken up in acetonitrile to give 2.12 g of the title compound, m.p. 215°C.

Example 33.

5 - (N - cyclopentyl - carbamoyl) - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine (386/1366). Operating as in Example 32, but employing cyclopentyl isocyanate, 3.46 g of the title compound, m.p. 225°C, are obtained.

Example 34.

5 - (N - cyclopentyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1360). Operating as in Example 2, but employing cyclopentyl isothiocyanate, the title compound, m.p. 185°C, is obtained in 60% yield.

Example 35.

5 - (N - cyclopropyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine (386/1359). A solution of 2.462 g of 4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine and 2.97 g of cyclopropyl isothiocyanate in 20 ml of acetonitrile is refluxed for 7 h. After evaporation to dryness, the residue is chromatographed on silica gel (ethyl acetate-ethanol as eluant) to give 1.42 g of the pure title compound, m.p. 185°C.

Example 36.

4 - Cyclohexyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1368). Operating as in Example 14, 15.5 g of 4-cyclohexyl-4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine, m.p. 150°C, are obtained from 18.4 g of histamine dihydrochloride and 24.4 ml of hexahydrobenzaldehyde. A solution of 2.05 g of 4 - cyclohexyl - 4,5,6,7 - tetrahydro-imidazo-[4,5-c]-pyridine and 1.1 g of methyl isothiocyanate in 30 ml of acetonitrile is refluxed for 5 h. The solution is cooled and filtered, and 2.50 g of the title compound, m.p. 232°C, are collected.

Example 37.

4 - Cyclohexyl - 5 - (N - isopropyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine. (386/1367). Operating as in Example 36, 2.53 g of the title compound, m.p. 218°C are obtained from 2.05 g of 4-cyclohexyl - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine and 1.52 g of isopropyl isothiocyanate.

Example 38.

4 - (2 - thienyl) - 5 - N - isopropyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine. (386/1369). Operating as in Example 14, 15 g of 4-(2-thienyl)-4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine, m.p. 170°C, are obtained from 18.4 g of histamine dihydrochloride and 18.4 ml of 2-thiophenaldehyde. A solution of 2.05 g of 4 - (2 - thienyl) - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine and 1.52 g of *iso*propyl isothiocyanate in 30 ml of acetonitrile is refluxed for 5 h. The solution is cooled and filtered: 2.18 g of the title compound, m.p. 205°C, are collected.

Example 39.

4 - (2 - thienyl)- 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine. (386/1383). Operating as in Example 38, the title compound is obtained in 66% yield, m.p. 215°C.

Example 40.

4 - (2 - furyl) - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine. (386/1372). Operating as in Example 14, 12 g of 4-(2-furyl)-4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine (oil) are obtained from 18.4 g of histamine dihydrochloride and 16.6 ml of furfural. A solution of 1.89 g of 4-(2-furyl)-4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine and 1.1 g of methyl isothiocyanate in 20 ml

of acetonitrile is refluxed for 5 h. The solution is cooled and filtered: 1.54 g of the title compound, m.p. 200°C, are collected.

Example 41.

4 - (2 - furyl) - 5 - (N - *iso*propyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine. (386/1373). Operating as in Example 40, 1.61 g of the title compound, m.p. 195°C, are obtained from 1.89 g of 4 - (2 - furyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine and 1.52 g of isopropyl isothiocyanate.

Example 42.

4 - Cyclohexyl - 5 - (N - methyl - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1374). Operating as in Example 28, 3.1 g of the title compound, m.p. 250°, are obtained from 4.1 g of 4-cyclohexyl - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

Example 43.

4 - Cyclohexyl - 5 - (N - *iso*propyl - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1375). Operating as in Example 29, 3.45 g of the title compound, crystallized from ethanol and melting at 254°, are obtained from 4.1 g of 4-cyclohexyl - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

Example 44.

4 - (2 - thienyl) - 5 - (N - *iso*propyl-carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1376). Operating as in Example 26, but employing isopropyl isocyanate, 2.3 g of the title compound, crystallized from ethanol and melting at 223° (dec.), are obtained from 3.5 g of 4-(2-thienyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

Example 45.

4 - Isopropyl - 5 - (N - *iso*propyl - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1377). Operating as in Example 26, but employing *iso*propyl isocyanate, 2.8 g of the title compound, crystallized from acetonitrile and melting at 202°C, are obtained from 2.48 g of 4-isopropyl-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

Example 46.

4 - (2 - thienyl - 5 - (N - methyl - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1378). Operating as in Example 26, 1.14 g of the title compound, crystallized from acetonitrile and melting at 230°, are obtained from 3.5 g f 4-(2-thienyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

Example 47.

4 - (2 - furyl) - 5 - (N - methyl - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1379). Operating as in Example 26, 1.55 g of the title compound, crystallized from acetonitrile and melting at 205°, are obtained from 1.89 g of 4-(2-furyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

Example 48.

4 - (2 - furyl) - 5 - (N - *iso* - propyl-carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine (386/1382). Operating as in Example 26, but employing isopropyl isocyanate, 2.23 g of the title compound, crystallized from acetonitrile and melting at 237° (dec.), are obtained from 2.84 g of 4-(2-furyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

Example 49.

3 - Methyl - 4 - ethyl - 5 - (N - *iso*propyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine (386/1391). Operating as in Example 17, the title compound crystallized from ethanol and melting at 196°, is obtained in 50% yield.

Example 50.

4 - Phenyl - 5 - amidino - 4,5,6,7 - tetrahydro - imidazo - [4,5 - c] - pyridine (386/1401). Operating as in Example 20, the monohydrochloride of the title compound, crystallized from ethanol and melting at 288° (dec.), is obtained in 80% yield.

Example 51.

4 - Cyclohexyl - 5 - amidino - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine (386/1405). Operating as in Example 20, the monohydrochloride of the title compound, crystallized from ethanol and melting at 305° (dec.), is obtained in 60% yield.

WHAT WE CLAIM IS:—

1. A process of preparing a compound of formula I as herein defined in which X is S, which comprises condensing an appropriate 4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine with an appropriate alkyl isothiocyanate in ethanol, acetonitrile or dioxan as solvent under reflux for from 4 to 12 hours.

2. A process of preparing a compound of formula I as herein defined in which X is O or NR_4 where R_4 is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, an amino, cyano, nitro or acylamino group which comprises condensing an appropriate 4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine with an appropriate alkyl isocyanate or substituted S-methyl isothiourea in ethanol, acetonitrile or dioxan as solvent under reflux for from 4 to 12 hours.

3. A process according to claim 1 substan-

tially as herein described in any of Examples 1 to 18.

4. A process according to claim 2 substantially as herein described in any of Examples 19 to 33.

5. A process according to claim 1 or 2 substantially as herein described in any of Examples 34 to 51.

6. A compound of formula I as herein defined prepared by a process according to claim 1 or claim 3.

7. A compound of formula I as herein defined prepared by a process according to claim 2 or claim 4.

8. A compound of formula I as herein defined prepared by a process according to claim 4.

9. 5 - (N - methyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

10. 5 - (N - ethyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

11. 5 - (N - *n* - propyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

12. 5 - (N - *iso* - propyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

13. 5 - (N - *n* - butyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

14. 5 - (N - cyclohexyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

15. 4 - Ethyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

16. 5 - (N - allyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

17. 4 - Ethyl - 5 - (N - isopropyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

18. 4 - Ethyl - 5 - (N - allyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

19. 4 - Ethyl - 5 - (N - butyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

20. 4 - Phenyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

21. 4 - Phenyl - 5 - (N - isopropyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

22. 4 - *Iso* - propyl - 5 - (N - methyl-thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

23. 4 - *Iso* - propyl - 5 - (N - *iso* - propyl-thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

24. 3 - Methyl - 5 - (N - methyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

25. 3 - Methyl - 5 - (N - *iso* - propyl-thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

26. 5 - (N - Phenyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

27. 5 - (N - Cyano - N' - methyl-amidino) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

28. 5 - Amidino - 4,5,6,7 - tetrahydro-imidazo - [4,5 - c] - pyridine.

29. 4 - Ethyl - 5 - amidino - 4,5,6,7-tetrahydro - imidazo - [4,5 - c] - pyridine.

30. 4 - Ethyl - 5 - (N - ethyl - amidino)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

31. 4 - Ethyl - 5 - (N - isopropyl-amidino) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

32. 5 - (N - ethyl - amidino) - 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

33. 5 - (N - *iso* - propyl - amidino)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

34. 4 - Phenyl - 5 - (N - methyl - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

35. 4 - Phenyl - 5 - (N - *iso* - propyl-carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

36. 4 - Ethyl - 5 - (N - methyl - carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

37. 4 - Ethyl - 5 - (N - *iso* - propyl-carbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

38. 5 - (N - methyl - carbamoyl) - 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

39. 5 - (N - *iso* - propyl - carbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

40. 5 - (N - cyclopropyl - carbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

41. 5 - (N - cyclopentyl - carbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

42. 5 - (N - cyclopentyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

43. 5 - (N - cyclopropyl - thiocarbamoyl)-4,5,6,7 - tetrahydro - imidazo - [4,5 - c]-pyridine.

44. 4 - Cyclohexyl - 5 - (N - methyl-thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

45. 4 - Cyclohexyl - 5 - (N - *iso* - propyl-thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

46. 4 - (2 - thienyl) - 5 - (N - *iso*-propyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro-imidazo-[4,5-c]-pyridine.

47. 4 - (2 - thienyl) - 5 - (N - methyl-thiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

48. 4 - (2 - Furyl) - 5 - (N - methylthiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

49. 4 - (2 - Furyl) - 5 - (N - *iso* - propylthiocarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

50. 4 - Cyclohexyl - 5 - (N - methylcarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

51. 4 - Cyclohexyl - 5 - (N - *iso* - propylcarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

52. 4 - (2 - Thienyl - 5 - (N - *iso* - propylcarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

53.4 - Isopropyl - 5 - (N - *iso* - propylcarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

54. 4 - (2 - Thienyl) - 5 - (N - methylcarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

55. 4 - (2 - Furyl - 5 - (N - methylcarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

56. 4 - (2 - Furyl) - 5 - (N - *iso* - propylcarbamoyl) - 4,5,6,7 - tetrahydro - imidazo-[4,5-c]-pyridine.

57. 3 - Methyl - 4 - ethyl - 5 - (N - *iso*-propyl - thiocarbamoyl) - 4,5,6,7 - tetrahydro-imidazo-[4,5-c]-pyridine.

58. 4 - Phenyl - 5 - amidino - 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

59. 4 - Cyclohexyl - 5 - amidino - 4,5,6,7-tetrahydro-imidazo-[4,5-c]-pyridine.

60. A compound of general formula I as herein defined in which X is S or a pharmaceutically acceptable acid addition salt thereof.

61. A compound of general formula I as herein defined in which X is O or NR_4, where R_4 is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, an amino, cyano, nitro or acylamino group or a pharmaceutically acceptable acid addition salt thereof.

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